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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ASHEN, JON BENJAMIN	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 07/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/005,996	PARTRIDGE ET AL.	
	Examiner	Art Unit	
	Jon B. Ashen	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 May 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) *4,26 and 27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-25 and 28-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. Applicant's response filed 05/02/2005 has been fully considered. Rejections and/or objections not reiterated from the previous office action mailed 10/20/2005 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-31 are pending in this application. Claims 32-61 were cancelled by Applicant in the communication filed 05/02/2005. Claims 4, 26-27 were withdrawn from further consideration in the prior Action, pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 1-3, 5-25 and 28-31 are currently under examination.

Election/Restrictions

Response to Arguments

2. Applicant's election of Group I, claims 1-31, in the reply filed on 5/21/04, was acknowledged in the Action mailed 10/28/05 wherein the requirement for restriction, was made final because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement. Therefore, the election was treated as an election without traverse (MPEP § 818.03(a)).

Additionally, Applicants arguments filed 05/02/2005 (pg. 6) that claim 4 as amended is allowable and generic to claims 4 and 26-27 are not persuasive because claim 4, was withdrawn from prosecution as being drawn to a non-elected invention (see the Action mailed 10/28/2005) and has not been amended in the communication filed 05/02/2005.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1 and 3 (and claims 2, 5-25 and 28-31, which depend directly or indirectly from claims 1 or 3) are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In the instant case, claims 1 and 3 have been amended recite, "on a cell composing the blood brain barrier." One of skill in the art cannot determine what is meant by this claim limitation because one of skill in the art considers that the blood brain barrier is composed of many cells and cannot envision the metes and bounds of a claim drawn to a single cell that composes the entire blood brain barrier. Applicant's attention is drawn to pg. 7 of the communication filed 05/02/2005 which sets forth a Usage Note taken from dictionary.com which states that "the parts compose the whole" and that "Fifty states compose (or constitute or make up) the Union". Given the meaning set forth and relied upon by Applicant, the instant rejection is considered proper for the following reasons. Based on the abovementioned

"Usage Note", if Fifty states compose the union (e.g. "the whole") then each state is one of "the parts that composes the whole." By the same argument, then, if more than a single cell composes the blood brain barrier (e.g., "the whole") then a single cell of the blood brain barrier is one of "the parts that compose the whole" and itself, cannot "compose" the whole.

5. Claim 3 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 3 recites, "on a cell comprising the blood brain barrier" at the end of the last line. One of skill in the art cannot determine what is meant by this claim limitation because one of skill in the art considers that the blood brain barrier is comprised of many cells and cannot envision the metes and bounds of a claim drawn to a single cell that comprises the entire blood brain barrier.

6. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 recites the limitation "said composition" in line 6. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

Response to Arguments

7. Applicant's amendment of claims 1 and 3, see pg. 2, filed 05/02/2005, is sufficient to overcome the rejection of claims 1-3, 6-16, 18-24, and 28-30 under 35 U.S.C. 102(b) as being anticipated by Penichet et al. (1999; Reference 39, PTO-1449 filed 8/23/04, instant application).

8. Applicant's amendment of claims 1 and 3, see pg. 2, filed 05/02/2005, is sufficient to overcome the rejection of claims 1-3, 6-16, 18-24, and 28-30 under 35 U.S.C. 102(b) as being anticipated by Pardridge et al. 1995 (Reference 38, PTO-1449 filed 8/23/04, instant application).

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1-3, 5-25 and 28-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Penichet et al. 1999 (Reference 39, PTO-1449 filed 8/23/02, instant application) or Pardridge et al. 1995 (Reference 38, PTO-1449 filed 8/23/02, instant application) in view of Hnatowich 1999 (Reference 21, PTO-1449 filed 8/23/02, instant application), Kurihara et al. 1999 (Reference 27, PTO-1449 filed 8/23/02, instant application), Tavitian (1998, Reference 48, PTO-1449 filed 8/23/02, instant application) and Zhao (Reference 59, PTO-1449 filed 8/23/02, instant application).

Penichet et al. teach a method of *in vivo* systemic administration of an imaging reagent to rats (pg. 4424, col. 2 bridge 4425, col. 1) and detecting the quantity of a signal produced by the detectable label wherein the imaging reagent is [^{125}I]anti-TfR IgG3-CH3-AvPNA, that comprises an antisense PNA that specifically hybridizes to a region of the *rev* mRNA of human immunodeficiency virus 1 (HIV-1) that comprises a targeting ligand that is an anti-transferrin monoclonal antibody linked to a the PNA by an affinity tag that comprises avidin and biotin wherein the carboxyl terminal of the PNA is amidated (pg 4423, col. 1) and the 5' terminal is biotinylated wherein the imaging reagent comprises a detectable label that is radiolabeled tyrosine [^{125}I].

Pardridge et al. disclose a method of *in vivo* systemic administration of an imaging reagent to rats and detecting the quantity of a signal produced by the detectable label (pg. 5593, col. 1) wherein the imaging reagent is [^{125}I]-biotin-PNA/OX26-SA conjugate, that comprises an antisense PNA that specifically hybridizes to a region of the *rev* mRNA of human immunodeficiency virus 1 (HIV-1) that comprises a targeting ligand that is an anti-transferrin monoclonal antibody linked to a the PNA by an affinity tag that comprises streptavidin and biotin wherein the carboxyl terminal of the PNA is amidated (pg 4423, col. 1) and the 5' terminal is biotinylated wherein the imaging reagent comprises a detectable label that is radiolabeled tyrosine [^{125}I].

Neither Penichet et al. nor Pardridge et al. teaches a method of imaging *in vivo* expression of a gene in a brain cell in a vertebrate wherein said first nucleic acid specifically hybridizes to said second nucleic acid or detecting the presence or quantity of a signal produced by the detectable label in brain cells wherein the presence or quantity of said label indicates the presence or quantity of a nucleic acid transcribed from said gene (amended claim 1) wherein the imaging reagent comprises a targeting ligand that is an antibody that specifically binds to an insulin receptor (claims 5 and 25), wherein said nucleic acid is labeled with a radiolabeled amino acid that is 111-indium or wherein said vertebrate is a human (claim 31).

Kurihara et al. teach the directed targeting of an EGF peptide radiopharmaceutical to image brain tumors *in vivo* wherein delivery is enabled to undergo transport thru the blood brain barrier (BBB) because of conjugation to a peptidomimetic mAb (monoclonal antibody) that transcytoses thru the BBB and the EGF

peptide is radiolabeled with [^{111}In]-labeled radionuclide chelated to EGF via a DTPA linker attached to lysine wherein the radiolabeled EGF is conjugated to a target delivery system via a biotin/streptavidin affinity groups (pg 6159, col. 1; pg. 6161, col. 2, 3rd paragraph). Kurihara et al. teach that the human EGFR (EGF receptor) binds both EGF and transforming growth factor alpha and that once internalized, EGF remains bound to the EGFR (pg. 6162, col. 2, top). Kurihara et al. teach that their studies demonstrate that "peptide radiopharmaceuticals such as EFG can be used to image brain tumors when the molecules are conjugated to a BBB drug delivery system (pg 6162, column 2, 2nd paragraph) and that "Although the OX26 mAb is specific for rats, similar studies can also be performed in humans using BBB transport vectors that bind to human BBB receptors. A mAb to the human insulin receptor is active in humans and Old World primates, such as the Rhesus monkey, and has a BBB transport coefficient 9-fold greater that that found with anti-TfR mAbs. In addition to neuroimaging brain tumors, the use of a BBB drug delivery system and a peptide pharmaceutical could also be directed toward therapy of human brain tumors" (pg. 6163, col. 1) and that "Virtually any neurodiagnostic or neurotherapeutic agent can be conjugated to the BBB drug delivery system for non-invasive brain drug delivery *in vivo*" (pg. 6163, col. 1, last sentence).

Hnatowich 1999, in regards to antisense applications beyond chemotherapy teaches that "Antisense is also becoming useful as a research tool in molecular biology" (pg 693. col. 2, 2nd paragraph) and that "In the development of new radiopharmaceuticals, high specificity and high affinity of binding have always been

recognized as useful properties. Accordingly, several potential applications of radiolabeled DNA as radiopharmaceuticals have been suggested. One nuclear medicine application, now obvious, involves the localization of radioactivity for imaging in tissues targeted by antisense mechanisms (i.e., antisense imaging) (pg 694, col. 1 bridge to col. 2) and that "To achieve therapy or imaging, antisense DNAs must cross the cell membrane and enter the cytoplasm" (pg. 696, col. 1, 4th paragraph) and that "It is hoped that the problem of poor cellular transport is soon resolved thereby removing perhaps the biggest hurdle to progress in antisense chemotherapy and, especially, to the development of antisense imaging (pg. 696, col. 2, 3rd paragraph). Hnatowich teaches that, "Obviously, it will also be useful to target diseases that may be of limited interested for chemotherapy, such as ischemic heart disease and renal insufficiency. Moreover, it may be of interest to image the expression of mRNAs which may be involved in normal cellular function and therefore ineligible for treatment (pg. 699, col. 2). Hnatowich teaches that "Most radioisotopes used in nuclear medicine are metals. One straightforward approach to radiolabeling DNAs with metallic radionuclides is first to derivatize the antisense DNA on either of its ends with a primary amine, possibly attached by a suitable linker to minimize steric hindrance. The amine then may be conjugated with various metal bifunctional chelators such as anhydrides of diethylene-triamine pentaacetic acid (DTPA).... [S]ingle stranded DNAs have been radiolabeled in this manner with ^{67}Ga, ^{111}In and ^{153}Sm" (pg. 699 bottom of col. 2 bridge to pg 700, top of col. 1) and that "Clearly, antisense imaging would be an extremely valuable diagnostic

tool, since, in theory, almost any tissue or disease state could be selectively imaged" (pg. 701, col. 2, 2nd paragraph).

Tavitian et al. teach that "Owing to their ability to block gene expression at the RNA level *in vivo*, antisense oligonucleotides are promising new pharmaceuticals" (pg. 467, col. 1, line 1) and that due to the need to chemically modify natural oligonucleotides to avoid rapid degradation and non-specific binding and to allow membrane passage, "[d]ozens of chemical alterations of the phosphodiester-deoxyribose backbone have been proposed, aimed at improving the pharmaceutical properties.... And that "Obviously, however, chemical modifications that modify sensitivity to nucleases, membrane passage, protein binding, etcetera, of the oligonucleotide should induce major alterations of its pharmacokinetics, whose knowledge is essential to evaluate its biological activity. Hence, a method allowing the measurement of the pharmacokinetics of oligonucleotides *in vivo* would offer significant progress in evaluating the efficiency of strategies being developed to deliver oligonucleotides to target tissues for therapeutic purposes (pg. 467, col. 1, 2nd paragraph).

Zhao et al. teach the wide spread expression of insulin receptor (IR) mRNA in rat brain cells (pg. 34895, col. 2) wherein they disclose findings from in situ hybridization, immunohistochemistry and immunoblotting experiments that confirm that IR is abundantly distributed in the brain (pg. 7, col. 1).

It would have been obvious to one of ordinary skill in the art to practice a method of imaging *in vivo* expression of a gene in a brain cell in a vertebrate comprising a)

administering an imaging reagent comprising a detectable label attached to a first nucleic acid that specifically hybridizes to a second nucleic acid transcribed from said gene where the first nucleic acid is linked to a targeting ligand that binds a receptor on a cell of the blood brain barrier, crosses said barrier, enters a brain cell (as taught by Penichet et al. or Pardridge et al.) and wherein said first nucleic acid specifically hybridizes to said second nucleic acid (as taught by Hnatowich) and b) detecting the presence or quantity of a signal produced by the detectable label in brain cells wherein the presence or quantity of said label indicates the presence or quantity of a nucleic acid transcribed from said gene (as taught by Hnatowich) wherein said nucleic acid is an antisense peptide nucleic acid (PNA) that bears a protecting group wherein the targeting ligand is a monoclonal antibody that specifically binds to a receptor on a cell of the blood brain barrier, crosses said barrier and enters a brain cell, wherein the first nucleic acid is linked to the targeting ligand by an affinity tag that comprises a biotin and an avidin (or streptavidin) wherein the PNA comprises a carboxyl terminal that is amidated wherein the detectable label is a radiolabeled amino acid that is tyrosine labeled with ^{125}I wherein the gene encodes a structural protein wherein the method comprises systemic administration of the imaging reagent to a living organism that is a vertebrate, a mammal or a non-human mammal (as taught by Penichet et al. or Pardridge et al.), wherein the imaging reagent is modified and comprises a targeting ligand that is an antibody that specifically binds to a human insulin receptor, as taught by Kurihara et al. and Zhao et al.), and the nucleic acid is a PNA (which is considered a peptide pharmaceutical) labeled with a radiolabeled amino acid that is 111-indium

attached to lysine via a DTPA linker as taught by Kurihara et al. and Hnatowich (now considered a peptide radiopharmaceutical or, at a minimum, a radiopharmaceutical), in order to image tissues targeted by antisense mechanisms, as taught by Hnatowich, and to measure the pharmacokinetics of oligonucleotides *in vivo* and evaluate their delivery as taught by Tavitian et al.

One of ordinary skill in the art would have been motivated to practice the method of the instant invention as taught by Penichet et al. or Pardridge et al., further comprising the limitations as taught by Kurihara et al., Zhao et al. and Hnatowich because, as taught by Kurihara et al., "Virtually any neurodiagnostic or neurotherapeutic agent can be conjugated to the BBB drug delivery system for non-invasive brain drug delivery *in vivo*" (pg. 6163, col. 1, last sentence), because antisense nucleic acids can be used as neurodiagnostics (as taught by Hnatowich), because conjugation of an antisense neurodiagnostic to a BBB drug delivery system could overcome the recognized obstacles facing the delivery of naked antisense chemotherapeutics (as taught by Hnatowich) and because, as also taught by Hnatowich, "Clearly, antisense imaging would be an extremely valuable diagnostic tool, since, in theory, almost any tissue or disease state could be selectively imaged" (pg. 701, col. 2, 2nd paragraph).,

One of ordinary skill in the art would have expected success in practicing the method of the instant invention as taught by Penichet et al. or Pardridge et al., further comprising the limitations as taught by Kurihara et al., Zhao et al. and Hnatowich because Penichet et al. and/or Pardridge et al. teach the successful administration of nucleic acid-targeting ligand constructs which are transcytosed thru the BBB and are

endocytosed by TfRs expressed on the surface of brain cells, because studies can be performed in humans using BBB transport vectors that bind to human BBB receptors using a mAb to the human insulin receptor that is active in humans and Old World primates, such as the Rhesus monkey, and has a BBB transport coefficient 9-fold greater that that found with anti-TfR mAbs (as taught by Kurihara et al.), because the insulin receptor is expressed on brain cells (as taught by Zhao et al.), because "Virtually any neurodiagnostic or neurotherapeutic agent can be conjugated to the BBB drug delivery system for non-invasive brain drug delivery *in vivo*" (as taught by Kurihara et al.) and because antisense nucleic acids can be formulated to target specifically expressed mRNAs with high specificity and high binding affinity (as taught by Hnatowich).

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

12. Applicant's arguments filed 05/02/2005 have been fully considered but they are not persuasive for the reasons of record as set forth in the Action mailed 10/28/2005 and clarified further herein.

Applicant has argued that the combination of the cited art fails to provide all the elements of the claimed invention and also fails to provide a reasonable expectation of success (pg. 10, final paragraph). Applicant has argued that the presently pending claims are directed to methods of imaging *in vivo* expression of a gene in a brain cell of

a vertebrate and that in order to image gene expression *in vivo*, the construct used in the presently claimed methods must cross two barriers in series -- The blood brain barrier (BBB) and the membrane of a brain cell. In addition, the construct must cross these barriers in sufficient quantity that *in vivo* imaging is possible and that the methods disclosed in the cited art:

1) Do not show constructs crossing both the blood brain barrier and the cell membrane;

2) Do not show hybridization of such constructs to gene transcripts (mRNA) *in vivo*; and

3) Do not establish a reasonable expectation of success (pg. 11).

Applicant has argued that the construct of Penichet et al. has no target with which to hybridize (pg. 11). Based on Applicant's amendment of the claims in the communication filed 05/02/2005, this argument is correct. However, Applicant's arguments as they pertain to the outstanding rejection are presented as if the outstanding rejection were under 35 U.S.C. § 102. An argument that a given reference, however, taken individually or even in combination with another reference, that is not in combination with all references, fails to provide a teaching of the claimed invention taken as a whole, is not persuasive because the basis of the rejection under 35 U.S.C. § 103(a) is that the prior art references, taken as a whole, render obvious the invention as set forth in the instant claims. Penichet et al. is not relied upon to teach, individually, each and every limitation of the instantly claimed method. In particular, Penichet et al. is not relied upon for a teaching of a transcribed nucleic acid that is specifically hybridized in the instantly claimed method, but rather this teaching is taken from the disclosure of Hnatowich (see below).

Applicant has also argued that while Penichet et al. alleges that the construct crosses the blood brain barrier (BBB), this reference does not establish that the construct crosses a cell membrane or that the construct appears in the cytosol of a brain cell in sufficient quantity to permit detection of gene expression because the brain tissues of Penichet et al. were removed and solubilized before scintillation counting, which indicates that any extracellular construct would be included in this measurement and that consequently Penichet et al. fails to establish that the construct crosses both the BBB and the cell membrane. However, this argument is not persuasive because, as stated on pg. 50, lines 6-7 of the instant specification, "the transferrin receptor (TfR) is expressed at both the BBB and the BCM" (*brain cell membrane* – added by Examiner for clarification of the abbreviation). Therefore, Penichet et al. do teach a construct that crosses the a cell membrane and that will appear in the cytosol of a brain cell because the transferrin antibody conjugated to the antisense nucleic acid of Penichet et al. was, absent evidence to the contrary, inherently transcytosed across the cell membrane of the BBB by the transferrin receptor expressed at the BBB and endocytosed into a brain cell by the transferrin receptor expressed at the BCM.

Applicant's has argued that Penichet et al. teach away from the claimed method because they teach extraction and solubilization of brain tissue and that, "In view of the unpredictability of the art (prior to the examples provided in the present specification), the failure to establish passage of the PNA construct across the membrane of a brain cell, the failure to show hybridization of the PNA to a gene transcript in a brain cell, Penichet6 et al. both fails to provide the presently claimed invention and fails to offer a

reasonable expectation of success (i.e., that a construct such as that recited in the pending claims could cross both the BBB and a brain cell membrane in sufficient quantity to hybridize to a target nucleic acid and produce a detectable signal" (pg. 12). In the first case, it is unclear what unpredictability of the art is being referred to by Applicant above because Applicant has only asserted unpredictability and not provided any indication of what this unpredictability may be. Moreover, Applicant's arguments are not persuasive for the reasons above because Applicant appears to be arguing the outstanding rejection as if it were under 35 U.S.C. § 102. The teachings of Penichet et al. are not relied upon to teach each and every limitation of the instant claims, however, they are considered, despite Applicant's assertion, to teach passage of a PNA construct across the membrane of a brain cell and are not relied upon to teach hybridization to a gene transcript in a brain cell.

Applicant has argued that "these defects are not remedied by the remaining references" and that Pardridge et al. offers essentially the same teaching as Penichet et al. in disclosing essentially the same construct which has an anti HIV-1 rev PNA coupled to the OX26 streptavidin conjugate and simply demonstrates that the construct crosses the BBB (pg. 12). However, this argument is not persuasive because, as stated on pg. 50, lines 6-7 of the instant specification, "the transferrin receptor (TfR) is expressed at both the BBB and the BCM" (*brain cell membrane* – added by Examiner for clarification of the abbreviation). Additionally, the disclosure of the instant specification indicates that the OX26 mAb binds the BBB TfR (pg. 47, [0150]) and that the antisense imaging agent of the instant invention is comprised of four domains

wherein the first domain is a peptidomimetic mAb that targets the TfR, which is expressed on both the BBB and tumor cell membrane and that the TfR is expressed on brain cells (pg. 43, [0144]). Therefore, Pardridge et al. do teach a construct that crosses the a cell membrane and that will appear in the cytosol of a brain cell because the OX26 mAb conjugated to the antisense nucleic acid of Pardridge et al. was, absent evidence to the contrary, inherently transcytosed across the cell membrane of the BBB by the transferrin receptor expressed at the BBB and endocytosed into a brain cell by the transferrin receptor expressed at the BCM.

Applicant has also argued that Pardridge et al. make no mention in regards to the uptake into brain cells of the construct or of the hybridization to a gene transcript within brain cells because the only measure of hybridization was performed *in vitro* (pg. 13, top). However, Applicant's arguments are not persuasive for the reasons above because Applicant appears to be arguing the outstanding rejection as if it were under 35 U.S.C. § 102. Pardridge et al. is not relied upon to teach each and every limitation of the instant claims and is not relied upon to teach the hybridization to a gene transcript within brain cells. Additionally, it is not clear what Applicant is arguing in stating that Pardridge et al. makes no mention in regards to uptake into brain cells because, in being conjugated to an anti-TfR antibody, the antisense PNA construct of Pardridge et al. was taken up into brain cells (as discussed above) and the specific recitation of this inherent property of the TfR (to mediate endocytosis) is not required for the reference to teach this limitation.

Applicant has argued that the combination of Penichet et al. and Pardridge et al. fails to provide the presently claimed invention or and fails to offer a reasonable expectation of success (i.e., that a construct such as that recited in the pending claims could cross both the BBB and a brain cell membrane in sufficient quantity to hybridize to a target nucleic acid and produce a detectable signal) (pg. 13, 2nd full paragraph). However, Applicant's arguments are not persuasive because Applicant appears to be arguing that a cited reference, taken in combination with another reference, that is not in combination with all references, fails to provide a teaching of the claimed invention as a whole. However, the outstanding rejection under 35 U.S.C. § 103(a) is based on the teaching of the prior art references taken as a whole.

Applicant has argued that the remaining cited references fail to remedy "these defects" which appears to be a reference to the failure of the remaining references to provide the presently claimed invention or to offer a reasonable expectation of success (pg. 13, 3rd full paragraph). In particular, Applicant has argued that Kurihara et al., disclose the use of an anti-TG-EGF construct where the EGF is radiolabeled with ^{111}In, that this construct contains no nucleic acid and that the EGF receptor is found on the surface of a cell and that binding of the EGF to its cognate receptor does not require the construct to cross the cell membrane and that therefore, Kurihara et al. offers no teaching regarding the ability of a nucleic acid containing construct to cross both the BBB and a cell membrane, to hybridize to a target inside a cell or to be present inside a cell in sufficient quantity to permit detection of gene expression.

However, Applicant's arguments are not persuasive for the reasons above and because the teachings of Kurihara are not relied upon, as if this rejection were being made under 35 U.S.C. § 102, to provide a nucleic acid construct, but, as reiterated from the outstanding rejection, to demonstrate that imaging of brain tumors can be performed using labeled pharmaceuticals and that "Virtually any neurodiagnostic or neurotherapeutic agent can be conjugated to the BBB drug delivery system for non-invasive brain drug delivery *in vivo*" (pg. 6163, col. 1, last sentence). In the case of Kurihara et al. the labeled pharmaceuticals are peptide radiopharmaceuticals but, as stated by Kurihara et al., "Virtually any neurodiagnostic or neurotherapeutic agent" can be used. Kurihara et al. is not relied upon to teach each and every limitation of the instant invention. Additionally, contrary to Applicant's assertion that the EGF receptor is found on the surface of a cell and that binding of the EGF to its cognate receptor does not require the construct to cross the cell membrane, the EGFR is involved in receptor mediated endocytosis and the binding of EGF to its cognate receptor will initiate that cellular process, absent evidence to the contrary.

In regards to Hnatowich, Applicant has noted that this cited reference discusses the use of labeled nucleic acids for imaging applications but has argued that this reference does not disclose the use of labeled nucleic acids attached to a targeting ligand as presently claimed (pg. 13, final paragraph). However, Applicant's arguments are not persuasive for the reasons above because Applicant appears to be arguing the outstanding rejection as if it were under 35 U.S.C. § 102. Hnatowich is not relied upon

to teach each and every limitation of the instantly claimed invention and is not relied upon to teach the use of labeled nucleic acids attached to a targeting ligand.

Applicant has argued that Hnatowich expressly teaches that *in vivo* imaging with labeled nucleic acids is problematic and provided excerpts from the cited reference (as listed on pg. 14 of the response). However, each of the provided excerpts does not address the outstanding grounds of rejection of the presently claimed method in view of the prior art references taken as a whole. In regards to the first 4 excerpts, provided by Applicant on pg. 14, each has been located in a section entitled "Antisense Concerns" on pg. 696 of the Hnatowich reference. This section details issues involved with delivery of naked antisense and therefore, do not teach away from the presently claimed antisense constructs because they do not address the issues involved with delivery of the presently claimed antisense constructs, but rather, issues related to the delivery of naked antisense nucleic acids. Moreover, these excerpts continue to provide motivation to modify naked antisense constructs to overcome the recognized prior art difficulties of delivering naked antisense across the BBB or to brain cells for the purposes of imaging. In regards to the excerpts on pg. 14 that are 5th and 6th from the top, these excerpts were located on pg. 701 of the Hnatowich reference. The excerpt beginning, "the purpose of this article" is again concerned with difficulties related to the delivery of naked antisense. The excerpt beginning "Existing methods" is related to radiolabeling with gamma emitters and is not considered relevant to the instantly claimed nucleic acid constructs that are required to practice the instantly claimed method because, as stated by Hnatowich on pg. 700, col. 1, bottom of the 2nd full

paragraph, "In general, encouraging results obtained in one study with ^{111}In labeled DNA suggest that radiolabeling of antisense DNAs with imageable (or therapeutic) radionuclides is unlikely to pose major problems.

Applicants conclusion, at the top of pg. 15, is that Hnatowich clearly teaches that antisense imaging is fraught with problems is acknowledged as it relates to methods that employ naked antisense. However, Applicant's arguments are not persuasive because the problems identified by Hnatowich in regards to the delivery of naked antisense are overcome by the combined teachings of the cited references in regards to the presently claimed antisense constructs that are conjugated to targeting ligands.

Applicant has argued, in regards to Tavitian et al. that these cited reference would also lead one of skill in the art to the conclusion that there was no reasonable expectation of success in practicing a method of *in vivo* imaging of gene expression in a brain cell using the presently described constructs and provided 4 excerpts on pg. 15. Applicant has argued that like Hnatowich, Tavitian et al. clearly teaches that effective imaging has not been accomplished and there are numerous difficulties to overcome and that therefore, Tavitian et al. establishes that there is no reasonable expectation of success for the presently claimed method. However, it is noted herein that, as in the response to Applicant's arguments in regards to Hnatowich, Applicants conclusion is acknowledged as it relates to the teachings of Tavitian et al. taken individually, in regards to methods that employ naked antisense. However, Applicant's arguments are not persuasive because the problems identified by Tavitian et al. in regards to the delivery of naked antisense are overcome by the combined teachings of the cited

references in regards to the presently claimed antisense constructs that are conjugated to targeting ligands.

In conclusion, Applicant's arguments overall are not considered persuasive because, contrary to Applicant's position, the combination of references cited fairly teaches and/or suggests the presently claimed method and does not establish, for the presently claimed nucleic acid constructs that are conjugated to targeting ligands, that there would be no reasonable expectation of success in practicing the instantly claimed method using the nucleic acid-targeting ligand constructs, as claimed.

Conclusion

13. No claims are allowed.

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon B. Ashen whose telephone number is 571-272-2913. The examiner can normally be reached on 7:30 am - 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached 0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Jba

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